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Randomised comparison between a loading and incremental dose model for ritodrine administration in preterm labour

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Objective To compare a new loading dose regimen for intravenous ritodrine administration in preterm labour with the conventional dose regimen.

Design Multicentre randomised trial using numbered opaque sealed envelopes.

Setting Five teaching hospitals in the Netherlands.

Participants Women ($n = 203$) in preterm labour at less than 34 weeks of gestation.

Interventions Women received either a loading dose ritodrine infusion followed, as soon as tocolysis was reached, by a decrease in infusion rate or the conventional schedule of increasing doses until uterine quiescence was achieved.

Results Frequency of successful tocolysis (71 %) and duration of treatment (55 h) were similar in both groups, but the loading dose schedule was better tolerated with fewer adverse events. Also the number of dose adjustments was smaller than in the incremental dose group ($P < 0{\cdot}001$). Overall, the differences between the two regimens were unexpectedly small.

Conclusions Despite the small differences, the loading model is easier to apply, requires fewer dose adjustments, is better tolerated with less side effects, and reduces the likelihood of clinical error.

INTRODUCTION

Classically, ritodrine, the most commonly used betamimetic agent for treatment of preterm labour, is administered intravenously in stepwise incremental doses until uterine quiescence is achieved or side effects preclude further increases[1,2]. This approach results in a gradual increase in plasma ritodrine concentrations that continues even after an effective infusion rate has been reached[3]. Because adverse effects are related to both total dose and dose changes[1,5] we designed a loading dose schedule with two main characteristics[6]. It avoids doses in excess of those needed to achieve and maintain uterine quiescence and it requires only one or two adjustments of the infusion rate to reach an effective minimal infusion rate[6].

We now report on a multicentre randomised study in which the new loading dose regimen was compared with the conventional system of ritodrine administration for treatment of preterm labour.

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METHODS

Five teaching hospitals participated in this 4 year study (shorter at some hospitals) after ethical approval of a protocol that consisted of two parts. The first part, which is reported here, consisted of a randomized comparison between the loading dose (LD) and a conventional incremental dose (ID) regimen for intravenous ritodrine administration in preterm labour. The second part, which is reported separately, was a double-blind, placebo-controlled evaluation of sustained release ritodrine capsules for maintaining uterine relaxation in those women whose preterm labour had been arrested by these treatments (Fig. 1)[7]. Irrespective of whether they had received the LD or the ID schedule, women participating in the second part had an equal chance of being allocated blindly to placebo or sustained release ritodrine capsules. This implies that the influence of main-

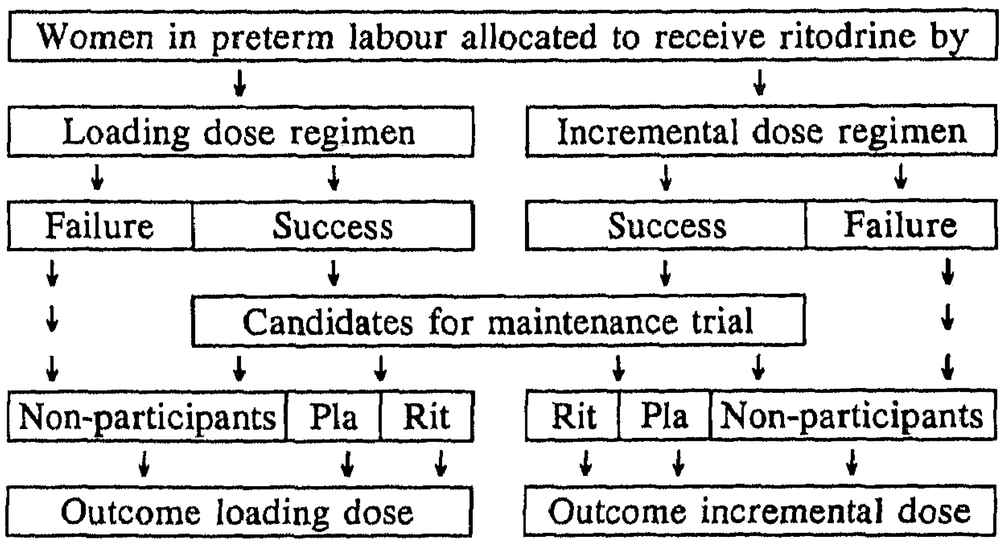

Fig. 1. Schematic representation of the study protocol (Pla = placebo; Rit = ritodrine).

tenance treatment (active or placebo) on neonatal outcome will be unbiased and similar for both the LD and ID schedules (Fig. 1).

A consecutive series of 203 healthy women in preterm labour, requiring tocolysis with beta-mimetics because of three or more regular contractions per 15 min and/or an increase in cervical dilatation before 34 weeks of gestation, participated in this study. After informed consent, women were allocated at random by numbered, opaque, sealed envelopes to either one of two treatment groups. Two additional envelopes were drawn erroneously for women who failed to meet the entry criterion of labour before 34 weeks and seven for women who had exclusion criteria, such as earlier tocolytic treatment in the current pregnancy ($n = 4$) or a diagnosis of intrauterine infection ($n = 1$), fetal anomaly ($n = 1$), or full dilatation ($n = 1$) before randomisation. These nine women were considered as nonparticipants prior to any assessment of outcomes.

Recruitment was stopped when the predetermined sample size of 200 women was known to have been achieved at the five centres. This sample size has an 80% power of detecting a 20% difference in the frequency of successful tocolysis between the two treatment groups ($\alpha = 0{\cdot}05$).

Women allocated to the experimental arm (LD; $n = 101$) received a loading dose of 200 μg/min ritodrine until tocolysis was reached whereupon the infusion rate was reduced in a standard fashion calculated from the interval between start of the treatment and tocolysis (Table 1). The conventional (ID; $n = 102$) treatment consisted of a dose of 50 μg/min ritodrine that was increased with 50 μg/min about every 15 min until uterine quiescence was reached or until side effects prohibited further dose increases. Both treatments were administered with an infusion pump. After cessation of uterine contractions, treatment was continued for 24 to 48 h in both groups. Thereafter, the dose was reduced to a maintenance level of

Table 1. Regimen used for ritodrine administration starting with a loading dose infusion rate of 200 μg/min.

Tocolysis achieved within (h)	Adapt dose to (μg/min)
Start infusion with 200 μg/min	
$\frac{1}{2}$	50
$\frac{1}{2}$–1	100
1–1$\frac{1}{2}$	150
1$\frac{1}{2}$–2	200
No tocolysis within 2 h: increase to 400 μg/min	
2–2$\frac{1}{2}$	250
2$\frac{1}{2}$–3	300
3–3$\frac{1}{2}$	350
3$\frac{1}{2}$–4	400
No tocolysis within 4 h: increase to 600 μg/min	
4–4$\frac{1}{2}$	450
4$\frac{1}{2}$–5	500
5–5$\frac{1}{2}$	550
5$\frac{1}{2}$–6	600

50 μg/min for 12–24 h whereupon oral maintenance treatment was started. The latter consisted of either placebo or sustained release capsules of ritodrine (240 mg daily), in a double-blind fashion, for seven days[7].

Treatment, whether intravenous or oral, was stopped in the event of severe side effects, signs of intrauterine infection or fetal distress, and imminent delivery. The use of other tocolytic drugs was not allowed unless clinically indicated because of failure to respond to ritodrine treatment alone. All other concurrent medication was restricted with the exception of corticosteroid administration for fetal lung maturation which was recommended.

The main outcome parameter was successful tocolysis defined as the end of intravenous treatment in the absence of progressive labour or achievement of 34 weeks of gestation, whichever occurred first. Additional predefined outcomes were: the total dose of ritodrine administered, the duration of intravenous treatment until tapering off, infusion rates of ritodrine 12, 24 and 48 h after start of treatment, and the number of dose adjustments in the first 12, 24 and 48 h of treatment.

Assessments of safety and tolerance were made on the basis of adverse events, dose adaptations prompted by side effects, and changes in fetal heart rate, maternal heart rate and blood pressure between the start of the infusion and the first few hours of treatment. Plasma concentrations of sodium, potassium, chloride and bicarbonate were measured at the start of treatment and 8 to 16 and 24 to 40 h afterwards.

Before analysis, all data entry sheets were assessed by one of us (M.J.N.C.K.), blinded to

treatment allocation and neonatal outcome. Statistical analysis was performed in the SAS analysis system using Student's *t* test, Wilcoxon two sample test and the χ^2 or Cochran–Mantel–Haenszel χ^2 tests. The CIA program was used for confidence interval analysis[8].

RESULTS

In the five participating centres 212 envelopes were drawn for the 203 participants and nine non-participants. Two women were excluded from the analysis: one in the LD group because of lost case records and one in the ID group because she was erroneously started on the loading dose and was therefore withdrawn from the study by her obstetrician. Both women gave birth to live infants who survived.

The overall evaluation was performed on the data of the remaining 201 women of whom 100 had been allocated to the experimental (LD) schedule and 101 to the conventional (ID) schedule. The groups did not differ statistically in terms of age, gestational age, number of twins and triplets, Bishop score[9], tocolytic index[10], and incidence of ruptured membranes (Table 2). There were 95 women (47 %; 50 from the LD group and 45 from the ID group; n.s.) who subsequently participated in the double-blind maintenance trial (Fig. 1).

The loading dose schedule was always administered according to protocol (Table 1), but the incremental dose schedule was started with 100 μg per min in seven women and in only 30 % of the women ($n = 32$) was the time interval for dose augmentations strictly observed at 15 min; in the others the interval was longer at 20 ($n = 34$) or even 30 min ($n = 30$). This was because the participating clinicians were used to being more cautious with the conventional infusion scheme, often applying it in a more gradual way than officially prescribed. We accepted this as normal variation within the confines of clinical practice.

Successful tocolysis was defined as arrest of intravenous treatment in the absence of progressive labour or at reaching a gestational age of 34 weeks. Tocolysis was considered to be only partially successful if another agent (always indomethacin) had been co-administered at some stage. The incidence of successful tocolysis, partial success and failure were similar in both groups (Table 3). In eight women treatment was stopped because of suspected intrauterine infection ($n = 4$), abruption ($n = 2$) or fetal distress ($n = 2$), rendering an assessment in terms of successful or failed tocolysis meaningless (not ascertainable; Table 3).

The total amount of ritodrine used up to the start of tapering off did not differ between groups (Table 3). Also the mean infusion rates in μg/min at 12, 24 and 48 h after start of treatment were similar as was the duration of intravenous treatment until the start of maintenance (Table 3). Statistically there was a highly significant difference in the number of dose adjustments in the first 12, 24 and 48 h of treatment (Cochran–Mantel–Haenszel, $P < 0{\cdot}001$; Table 3). Side effects (Table 4) precluding further dose increments or prompting a lowering or even arrest of the infusion occurred significantly more often in the ID group (Cochran–Mantel–Haenszel, $P = 0{\cdot}02$; Table 3).

Starting with the relatively high loading dose (200 μg/min) in the LD group caused fewer complaints and side effects, than the low starting dose of the incremental scheme (50 μg/min) which had to be upgraded several times. In only one woman in the ID group was the infusion stopped in the first 12 h because of severe side effects (headache, dizziness, palpitations, tremor, dysp-

Table 2. Characteristics of women participating in the trial.

Characteristic	Loading dose ($n = 100$)	Incremental dose ($n = 101$)	*P* value*
Duration of pregnancy at trial entry			
$n < 28$ weeks	8	5	
$n < 32$ weeks	51	48	
Mean (SD)	217 (15)	219 (15)	0·27**
Prelabour rupture of the membranes	16	14	0·67†
Multiple pregnancy	10	9	0·79†
twin pregnancy	9	8	
triplet pregnancy	1	1	
Tocolytic index: mean (SD)	3·9 (1·8)	3·7 (1·7)	0·43††
Bishop score: mean (SD)	4·5 (2·3)	4·8 (1·9)	0·36††

*Statistical test used: ** *t* test, † χ^2 test, †† Cochran–Mantel–Haenszel.

Table 3. Characteristics and main outcomes of the two treatment schedules.

Characteristic	Loading dose ($n = 100$)	Incremental dose ($n = 101$)	P value*
Mean infusion rates in μg/min (SEM)			
At 12 h	151 (11)	166 (9)	0·08**
At 24 h	152 (11)	154 (8)	0·27**
At 48 h	159 (15)	165 (11)	0·25**
Treatment until tapering off: mean (SEM)			
Total dose of ritodrine (mg)	573 (97)	552 (67)	0·32**
Duration (h)	59 (8)	52 (4)	0·71**
Infusion rate adjustments (n)			
Within 12 h; mean (SEM)	0·9 (0·08)	2·3 (0·16)	< 0·001†
Between 12 and 24 h (SEM)	0·2 (0·06)	0·2 (0·05)	0·71†
Within 24 h: mean (SEM)	1·1 (0·11)	2·4 (0·20)	< 0·001†
Tocolytic effect			0·91†
Success	68	69	
Partial success	4	2	
Failure	25	25	
Not ascertainable	3	5	
Women with changes in infusion rate because of side effects (n)			0·02†
Warranted increase impossible	5	6	
Infusion rate reduced	2	9	
Infusion stopped	0	1	
Delivery			
Within 12 h	9	6	0·43††
Between 12 and 24 h	4	7	0·37††
Between 24 and 48 h	6	5	0·77††
< 32 weeks	20	21	0·89††
32–33 weeks	17	16	0·85††
34–36 weeks	24	16	0·11††
Mean gestational age (days; SEM)	248 (2·7)	250 (2·7)	0·59§

* Statistical test used: ** Wilcoxon test, † Cochran–Mantel–Haenszel, †† χ^2 test, § t test.

Table 4. Nature and frequency of maternal side effects in the first 12 h of the loading dose and incremental dose schedules.

Moderate or severe side effects	Loading dose ($n = 100$)	Incremental dose ($n = 101$)	Difference (%) and 95% CI
Any type of side effect	22	32	−9·6 (−21·7 to 2·5)
Palpitations	8	16	−7·8 (−16·6 to 1·0)
Tachycardia	7	8	−0·9 (−8·1 to 6·3)
Tremor	7	18	−10·7 (−19·6 to −1·9)
Agitation	4	3	1·0 (−4·0 to 6·0)
Nausea	5	4	1·0 (−4·6 to 6·7)
Vomiting	1	4	−2·9 (−7·2 to 1·3)
Headache	1	3	−2·0 (−5·8 to 1·9)
Dyspnea	1	1	0 (−2·7 to 2·7)
Total side effects (n)	34	57	

noea, tachycardia, nausea and agitation); she gave birth within 4 h of stopping treatment. In 22 other women (LD: 7; ID: 15) the infusion rate could not be increased or had to be lowered because of side effects (Table 3).

Changes in serum electrolytes and bicarbonate before and 8 to 16 and 24 to 40 h after the start of treatment did not differ between the groups. The largest change was seen in potassium levels which decreased significantly ($P < 0·001$) from before treatment in the entire group. Changes in chloride, sodium and bicarbonate were not remarkable.

Maternal heart rate and blood pressure were recorded more frequently in the ID group than in the LD group, because such measurements were often linked to adjustments in the infusion rate which were more frequent in the ID group. There were no statistically significant differences between the LD and ID group in maternal heart rate, increasing, respectively, by 30 and 27 beats per

Table 5. Perinatal and neonatal outcome after loading dose and incremental dose treatments.

Outcome	Loading dose ($n = 111$)	Incremental dose ($n = 111$)	Difference (%) and 95% CI
Fetal and neonatal mortality	1	4	−2·7 (−6·6 to 1·1)
Admission to intensive care	65	60	4·5 (−8·5 to 17·5)
Reasons for admission*			
Born too early	51	46	4·5 (−8·5 to 17·5)
Small for gestational age	15	7	7·2 (−0·6 to 15·0)
Fetal distress	6	10	−3·6 (−10·4 to 3·2)
Suspected infection	4	5	−0·9 (−6·1 to 4·3)
Sepsis	5	7	−1·8 (−7·8 to 4·1)
Others	13	18	−4·5 (−13·6 to 4·6)
Respiratory distress syndrome	12	17	−4·5 (−13·4 to 4·3)
Class I or II	11	14	−2·7 (−11·0 to 5·6)
Class > II	1	3	−1·8 (−5·3 to 1·7)
Patent ductus arteriosus	1	6	−4·5 (−9·1 to 0·1)
Periventricular–intraventricular haemorrhage	4	15	−9·9 (−17·2 to −2·7)
Grade I or II	4	12	−7·2 (−13·9 to −0·5)
Grades > II	0	3	−2·7 (−5·7 to 0·3)
Hyperbilirubinaemia	32	28	3·6 (−8·1 to 15·3)

* Some infants had several reasons for admission.

min, and in fetal heart rate which increased by 14 beats/min in both groups. Changes in or absolute levels of systolic blood pressures were not statistically different between both trial arms. The proportion of women with a drop in diastolic blood pressure was significantly greater in the ID group (LD: 49%; ID: 73%), but the extent of the decrease was similar for both groups. Changes in pulse pressure in both groups were comparable and of negligible clinical importance.

The proportions of women delivering before 32, 34 and 37 weeks were similar in both treatment groups (Table 3). Including 17 twin and 2 triplet pregnancies each treatment group contains 111 infants with mean birthweights of 2421 ± 784 g in the LD group and 2570 ± 879 g in the ID group.

There was one unexplained intrauterine death at term in the LD group eight weeks after stopping ritodrine treatment. Four neonatal deaths occurred in the ID group (Table 5); two of these were due to immaturity in a twin pregnancy (25 weeks), one to cord prolapse and one to hydrocephaly. There were no maternal deaths and no instances of pulmonary oedema.

The main neonatal morbidity was respiratory distress syndrome which occurred with equal frequency in both treatment groups (Table 5). Periventricular–intraventricular haemorrhage was less frequent in the LD group ($n = 4$) than in the ID groups ($n = 15$; Table 5), but a difference in this outcome was not a prior hypothesis of our study. All adverse infant outcomes except admission to neonatal intensive care and hyperbilirubinaemia tended to be more frequent in the ID group than in the LD group (Table 5).

DISCUSSION

As betamimetic agents are potent drugs that can cause severe adverse effects, it is important to limit the dose and duration of treatment to what is thought to be clinically useful[11]. From our previous work we had anticipated that the LD schedule would result in lower infusion rates and a smaller total amount of ritodrine than the conventional ID schedule recommended by the manufacturer.[6] While it is disappointing that this did not materialize, there is an explanation for it. Being aware of the potential hazards of ritodrine administration and the fact that side effects are associated nearly as much with changes in infusion rates as with the rates themselves, clinicians had become more cautious in their application of the conventional infusion schedule[4,5]. This was shown by the fact that clinicians tended to observe longer intervals between dose increments than the ID protocol prescribed. While increasing experience with the new loading dose regimen may have accentuated this tendency, data were not analysed before completion of the trial and there was no evidence that the incremental regimen was applied less conscientiously at the end than at the beginning of the trial.

Despite the more cautious approach in applying the conventional regimen, the loading dose schedule was still tolerated better, particularly during the initial and most crucial first 12 h of treatment.

On the whole, the incidence of all side effects was greater with the ID than with the LD schedule, but the difference was less pronounced than we had anticipated. We should point out that clinicians and pregnant women were not blinded to the treatment schedule and that only the analysis of data, but not their registration, occurred without knowledge of the treatment group.

As anticipated, tocolysis was reached with far fewer dose adjustments when using the LD rather than the ID schedule. This may have a beneficial effect in that each dose adjustment carries a risk of error. This is particularly important when the adjustment calls for an increase in infusion rate and when the clinical staff have relatively little experience with the use of this powerful agent.

On the whole, there was a trend for neonatal outcome to be better with the LD than with the ID schedule, but most of the difference is compatible with chance. There was a marked difference in the incidence of periventricular–intraventricular haemorrhage in favour of the LD regimen. This should be interpreted with caution as a difference in this outcome was not a prior hypothesis of the trial. Nevertheless, there could be a plausible mechanism in that virtually all cases were observed in infants born during or shortly after the arrest of ineffective tocolytic treatment. The immature brain is less well protected against acute fluctuations in blood pressure than the brain of the mature infant[12]. Van de Bor and Walther reported that there is only a narrow range of pressure over which cerebral blood flow in preterm infants remains relatively constant[13]. Thus, fluctuations in ritodrine levels to which infants, like their mothers, are exposed may be important. Betamimetic-induced increases in fetal cardiac output[14], particularly when combined with a redistribution to the upper body as suggested by Petersen *et al.*[15], may lead to significant increases in the perfusion pressure to various regions of the brain. While several studies found no significant associations between betamimetic drug treatment and the incidence of periventricular–intraventricular haemorrhage in preterm infants[16–18], others have reported a more than twofold increase in the incidence of periventricular–intraventricular haemorrhage in infants whose mothers had been treated with betamimetics[12]. The best data available originate from the randomised controlled trials of betamimetic treatment[19,20]. These do not indicate an increased risk of periventricular–intraventricular haemorrhage and the results of the largest trial are more likely to be compatible with a decrease rather than an increase in its incidence[20]. This does not necessarily exclude, though, that our present findings represent a true instead of a chance difference between the two treatment regimens. If this were so, it would constitute a major advantage for the loading dose regimen.

As the loading dose scheme is at least equally effective as the incremental dose schedule while needing fewer dose adjustments and being better tolerated in practice, we recommend the loading dose schedule as the preferred and safest of the two approaches to tocolytic treatment with ritodrine in preterm labour.

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